At the outset, Applicant has already overcome a 35 U.S.C. §112, first paragraph rejection. *See* Response to Office Action dated 8 May 2009. However, for completeness sake, Applicant again responds to the current rejection.

Claims 1 and 22 are directed to a method for preventive treatment of Parkinson's disease. The Examiner analyzes "preventive treatment of Parkinson's disease" using the Wands factors (MPEP 2164.01(a)). Taking each of these factors in turn, Applicant responds as follows. In the interest of brevity, Applicant's references to rotigotine herein are intended to encompass rotigotine or a pharmaceutically acceptable salt thereof as recited in Claims 1 and 22.

Nature of the Invention: Applicant agrees that Claims 1 and 22 generally pertain to a method for preventive treatment of Parkinson's disease. The present specification, at paragraph **[055]**, clearly defines "prevention" and "preventive treatment" of Parkinson's disease as encompassing not only preventing but delaying appearance or significant development of motor symptoms of the disease. The Office Action (p. 5) states "the instant claims are drawn to a composition and method of preventing all preclinical stages of any and all stages of Parkinson's disease, which includes any undetectable stages of the disease." The method of Claims 1 and 22 include identifying subjects without "clinically confirmed" Parkinson's disease, which means the patient population includes those that have less than two of the cardinal symptoms. Additionally, the specification as filed at paragraph **[0004]** (emphasis added) teaches that "[c]urrent clinical observations as well as anatomical and genetic research now show that it is possible to both diagnose patients with Parkinson's disease at an early stage and to identify high-risk patients" including, identifying eight (8) different diagnostic markers. The specification as filed also teaches that "[t]he earlier a therapy can be initiated, the greater the chances of a long-lasting prevention of the onset of symptoms that lower the quality of life." *See* the specification as filed at paragraph **[0006]**.

Breath of the Claims: The Office Action at p. 5 states "[t]he claims encompass prevention of a complex cell degenerative disorder in humans which has potentially many different causes (i.e. many different mutations or combinations of mutations). Each of which may or may not be addressed by the administration of the claimed compounds." While this may be true that there are potentially many different causes of Parkinson's disease, there is no

suggestion in the claims that administration of rotigotine can address such causes of Parkinson's disease, including mutations or combinations of mutations. What Applicant first discovered is that rotigotine reduced neuron loss and it is known that "patients with Parkinson's disease only develop the motor disturbances once approximately 70% to 80% of the dopaminergic neurons in the substantia nigra (SN) have been irreversibly damaged." In other words, early therapy can provide long-lasting prevention of irreversible damage to 70% to 80% of the dopaminergic neurons in the substantia nigra, thereby preventing clinically confirmed Parkinson's disease (or experiencing two or more of the cardinal symptoms).

Guidance of the Specification and working examples: The Office Action (p. 5) states that "[a]ll of the guidance provided by the specification is directed towards **treatment rather than prophylaxis** of dopaminergic cell loss (i.e. Parkinson's disease)." This is hardly the case. The majority of the specification is directed to neuroprotection. The Examiner even admits that "[t]he data presented [in the specification] just demonstrates the neuroprotective nature of rotigotine." *See* Office Action, p. 5. **Neuroprotection "prevents" Parkinson's disease**.

The Office Action also states that "[t]he examples recited in the instant disclosure recite[] treatment of animals in which experimental Parkinsonism's were generated by treating them with MPTP neurotoxin." "The MPTP model is [] deemed to be predictive of the required neuroprotective characteristics." *See* Dawson & Dawson (2002) Nature Neurosci. Suppl. 5:1058-1061,1059, col 1; *see also* the specification as filed at paragraph **[0014]**. "[N]europrotective agents need to be given prophylactically in the MPTP model." *See Id.* (emphasis added). In Embodiments 3 and 4 of the present specification, MPTP-treated mice exhibited 50-60% neuron loss, a level consistent with a subject not (or not yet) having clinically confirmed Parkinson's disease. In fact, Embodiment 4 (see paragraph **[0078]** of the specification as filed) shows that rotigotine was administered 16 hours before MPTP intoxication.

The specification as filed states "[t]he test results suggest that apoptotic processes are prevented by rotigotine" or simply put, the embodiments set forth in the specification establish that apoptotic processes believed to destroy dopaminergic neurons which causes motor disturbances in Parkinson's disease is prevented by rotigotine. *See* the specification as

filed at paragraph **[0015]**. Similarly, the specification (paragraph **[0019]**) reports findings from a study involving primates, which revealed, among other things, that "[t]he density of the nerve ending in the striatum [of monkeys treated with MPTP] was much higher than it was in the untreated animals." The results in the specification as filed show that rotigotine improved the survival of the neurons and the nerve endings in relation to the dose. Accordingly, because the working examples used are a well-established prophylactic model and the degree of neuron loss was indicative of prediagnostic stage of the disease, Applicant submits that the data are sufficient to demonstrate preventive action of rotigotine.

The State of the Prior Art: The Examiner acknowledges that:

> In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of Parkinson's disease" (see 26 Sept 2011 Office Action, p. 6).

At the outset, Applicant does not contest such statement. However, Applicant does contest the implication that since others have not done this, Applicant's specification as filed fails to enable long-lasting prevention of Parkinson's disease. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP 2164.01. As set forth in Table 2 and Figures 1 and 2, "rotigotine had a neuroprotective action: on the one hand, the number of degenerating neurons in the mesencephalon was reduced following the administration of rotigotine (Table 2) and on the other the dopaminergic innervation of the striatum is virtually completely retained or restored (Figures 1 and 2)" (paragraph **[0019]**, emphasis added). The Examples in the specification teach that if rotigotine is administered, neuron loss can be stabilized. The result of such stability is that a clinical diagnosis of Parkinson's disease (or early loss of pre- and postsynaptic dopaminergic neurons) is never made. Thus, although prior art may be limited on prevention of Parkinson's disease, one of ordinary skill in the art reading Applicant's invention disclosure, would not find it "highly unlikely" that administration of rotigotine to patients without clinically confirmed Parkinson's disease would result in long-lasting prevention of Parkinson's disease.

Amount of Experimentation Necessary. Contrary to the Examiner's assertions on p. 7

that the invention is directed to a combination and one of ordinary skill has to engage in undue experimentation to test the invention, Claims 1 and 22 are directed to a method and one of ordinary skill in the art does not need to engage in undue experimentation to prevent Parkinson's disease by administering rotigotine to a subject without clinically confirmed Parkinson's disease. The specification lays out the claimed method, for example, how to identify the subjects, how to administer rotigotine, the suitable dosages of rotigotine, and other active substances that rotigotine can be combined with. *See*, the specification as filed, at paragraphs **[0059]-[0065]**. No undue amount of experimentation is necessary to practice the invention as presently claimed, based on the disclosure in the present specification.

In summary, a correct analysis of the *In re Wands* factors leads to the conclusion that a method for preventive treatment of Parkinson's disease, as set forth in Claims 1, 3-4, 14-18, and 21-24, is fully enabled by the specification under 35 U.S.C. §112, first paragraph. Accordingly, as *Genetech* (42 USPQ2d 1001) held, Applicant should be rewarded for the search and invention.

Withdrawal of the present rejection is respectfully requested.

2. Rejection under 35 U.S.C. §103(a) over Li In View of Gerlach and Guttman

Claims 1, 3-4, 14-18, and 21-24 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 7,632,859 (herein "Li") in view of "Gerlach *et al.* (2003 referenced in instant IDS" (herein "Gerlach") and Guttman *et al.* (2003) Can. Med. Assoc. J. 168:293–301 (herein "Guttman"). This rejection is respectfully traversed.

Per the 2 December 2011 telephone conference with the Examiner, Gerlach referred to in the rejection is Gerlach *et al.* (2003) Neurotox. Res. 5:43-51 submitted in the last Information Disclosure Statement dated 14 Dec 2009 (as opposed to Gerlach (2003) J. Neural Transm 65:167-183 submitted in an Information Disclosure Statement on 28 Nov 2007).

Further, the publication date of Li (17 June 2004) is after the earliest priority date of the present application (24 December 2003). Li does not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Li constitutes prior art to the present invention under any section of 35 U.S.C. §102. Further, Li and the present application are commonly owned by UCB Pharma GmbH (by change-of-name from Schwarz Pharma AG). Applicant further reserves the right to disqualify Li as prior art against the

claimed invention under 35 U.S.C. §103(c).

Moreover, Gerlach (2003) and Guttman (4 Feb. 2003) are less than one year before the earliest priority date of the present application (24 December 2003). No admission is made herein that the disclosure of Gerlach and Guttman constitutes prior art to the present invention under any section of 35 U.S.C. §102. Applicant reserves the right to make a showing of earlier invention to disqualify Gerlach and Guttman.

However, regardless of the above, even if Li, Gerlach, and Guttman represented prior art to the present invention, Li, Gerlach, and Guttman, alone or in combination, do not render the present claims *prima facie* obvious, for reasons set forth below.

2.1. The Cited References Fail to Teach All Elements of Claim 1

The Office Action (p. 11) states "[i]t would be obvious to one of ordinary skill in the art to administer rotigotine to the subject who does not have clinically confirmed Parkinson's disease to provide neuroprotection against dopaminergic neuron loss because rotigotine is effective for the treatment of Parkinson's disease… ." The specification as filed at paragraph [0002] teaches several compounds that were known as "medicants for alleviating the ***motor symptoms***." However, the specification also teaches "Parkinson medicaments that only have **an effect on the symptoms do not promise any advantage with regard to the preventive treatment** of Parkinson's disease since they do not have any influence on the destruction of dopaminergic cells or on the progression and/or onset of the disease." *See* the specification as filed at paragraph [0010] (emphasis added). Just because a drug is effective for treating motor symptoms of Parkinson's disease, does not render obvious that the drug will also act as a neuroprotective agent, or prevent Parkinson's disease. It was Applicant who first discovered rotigotine was a neuroprotective agent and effective for patients without clinically confirmed Parkinson's disease.

(a) Neither Li Nor the Secondary Documents Disclose Preventive Treatment of Parkinson's disease.

Li teaches, among other things, treatment of Parkinson's disease with rotigotine. Li, however, does not discuss rotigotine having neuroprotective properties. *See* Office Action, at p. 10. Although the Office Action (p. 11) states "Gerlach et al teach that biochemical

markers, such as neuromelanin can be used or diagnostic markers in Parkinson's disease", it is not apparent how this is relevant to a method for preventive treatment of Parkinson's disease. Similarly, Guttman deals with the *treatment of symptoms* of Parkinson's disease, and not preventive treatment.

Accordingly, the cited art fails to disclose, teach or suggest a method for preventive treatment of Parkinson's disease.

(b) Neither Li Nor the Secondary Documents Disclose Treating a Subject Without Clinically Confirmed Parkinson's Disease.

Li and Guttman deal with the treatment of symptoms of Parkinson's disease in clinically confirmed Parkinson's disease patients. Gerlach deals with the role of neuromelanin and iron in Parkinson's disease. Thus, none of the cited documents suggest, teach or disclose treatment of patients without clinically confirmed Parkinson's disease.

To reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination. MPEP 2142. Since Applicant, for the first time provided that rotigotine is (1) a neuroprotective agent effective in preventing dopaminergic neuron loss in (2) subjects without clinically diagnosed Parkinson's disease, the Office Action has failed to cite documents or a combination of such that discloses, teaches or suggests a method for preventive treatment of Parkinson's disease in a subject without clinically confirmed Parkinson's disease.

2.2 Prophylactic Treatment of Parkinson's Disease is Unpredictable

The Office Action (p. 4) states that "[t]he nature of the invention is extremely complex." The Office Action (p. 6) also discusses the unpredictability in the art, by acknowledging "there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of Parkinson's disease." Further, the Examiner states in the Office Action dated 14 Sept. 2009 (p. 17):

> ...prophylactic treatment methods for Parkinson's disease are still unpredictable and there are no therapies available currently which delay the progression of PD.

Since there has to be "a finite number of identified, predictable solutions" to establish a presumption of *prima facie* obviousness, the Examiner's acknowledgement of unpredictability of prophylactic treatment of Parkinson's disease is an implicit acknowledgment by the Office that there is not "a finite number of identified, predictable solutions." *KSR International Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (emphasis added). For example, one of ordinary skill in the art would have to:

1. select one of the numerous drugs known to be effective in treating symptoms associated with Parkinson's disease (with no pattern of preference or guidance),
2. determine if the selected drug had a neuroprotective effect, and
3. determine the effect of treating subjects without clinically confirmed Parkinson's disease.

Finding a drug that met all three (3) categories could involve an infinite number of investigations and experimentations. Thus, at most, the cited documents provide no more than a "plan" or "invitation" for those skilled in the art to experiment – which is insufficient to establish *prima facie* obviousness. *See* MPEP 2164.06(b).

Unpredictability in prophylaxis of Parkinson's disease is further supported by:

- Nair *et al.* Biochem. J. 373:25-32 (2003) (emphasis added) which states that "certain DA agonists, **but not all**, could induce a robust increase in cell survival via activation of the D_2 receptors";
- Becker *et al.* (2002) J. Neurol. 249(Suppl. 3):III/40–III/48 by stating that "[a]t present, no treatment has proven to influence this progressive course of the disease by protecting neurons or by postponing cell death" and concludes "at present we have no therapeutic options for these subjects and, if we had any, different indications for early intervention would have to be established." *See* Becker, at p. III/40, III/45.
- Guttman (p. 297, bottom Col. 1) which emphasizes that "no therapies are proven to ... delay the progression of Parkinson's disease."; and

- Gerlach (2003) J. Neural Transm 65:167-183 by stating "there is increasing evidence for the view that PD is a multifactorial disorder and that the degeneration of dopaminergic neurons is the result of a number of synergistically interacting neurotoxic processes. The neuroprotective potential of the dopamine receptor agonists may thus be insufficient to produce a significant clinical effect." *See* Gerlach, at p. 178, *emphasis added.*

The above evidence of record, along with the Office's statements in the current Office Action, suggest that the "likely" outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for nonobviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for nonobviousness stronger.)

In this complex and unpredictable art, Applicant was the first to identify rotigotine as 1) a neuroprotective agent effective for preventive treatment of Parkinson's disease, and 2) in subjects without clinically confirmed Parkinson's disease. Accordingly, it could not have been predicted that rotigotine, although known to be effective in reducing symptoms of Parkinson's disease post-diagnosis, would prevent Parkinson's disease in subjects without clinically confirmed Parkinson's disease.

2.3 Conclusion: Rejection Under 35 U.S.C. § 103

Each of Claims 3-4, 14-18, 21, and 23-24 depends from and incorporates all limitations of Claim 1 or 22, respectively. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 3-4, 14-18, 21, and 23-24 is non-obvious over the cited art for at least the same reasons that Claim 1 or 22 is non-obvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Li in view of Gerlach and Guttman, is respectfully requested.

3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a

full and complete response has been made to the present Office Action and that the application is in condition for allowance. Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.

/ Leanne M. Rakers /

Leanne M. Rakers
Attorney for Applicant
Reg. No. 64,412
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
314-726-7518 (tel)
314-726-7501 (fax)